1073-075

BA

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 241/44, 498/04, 241/54 — A1

(11) International Publication Number: **WO 97/19934**

(43) International Publication Date: 5 June 1997 (05.06.97)

(21) International Application Number: PCT/HU96/00072

(22) International Filing Date: 28 November 1996 (28.11.96)

(30) Priority Data:
P 95 03422 30 November 1995 (30.11.95) HU

(71) Applicant *(for all designated States except US)*: CHINOIN GYÓGYSZER ÉS VEGYÉSZETI TERMÉKEK GYÁRA RT. [HU/HU]; Tó u. 1-5, H-1045 Budapest (HU).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: BATA, Imre [HU/HU]; Frankel Leó u. 7, H-1027 Budapest (HU). BÁTORI, Sándor [HU/HU]; Rákóczi F. út 268/A, H-1214 Budapest (HU). BENCE, Judit [HU/HU]; Szilvánus sétány 33, H-1031 Budapest (HU). BÖCSKEI, Zsolt [HU/HU]; Nyuszi sétány 3, H-1214 Budapest (HU). CSIKÓS, Éva [HU/HU]; Rákóczi 2110/6 hrsz., H-2095 Üröm (HU). ERDŐ, Sándor [HU/HU]; Kléh István u. 3/b, H-1126 Budapest (HU). GÖNCZI, Csaba [HU/HU]; Lisznyai u. 5, H-1016 Budapest (HU). HERMECZ, István [HU/HU]; Molnár u. 53, H-1056 Budapest (HU). HÉJA, Gergely [HU/HU]; Násznagy u. 27, H-1131 Budapest (HU). LAKICS, Viktor [HU/HU]; Pesti u. 63, H-1173 Budapest (HU). MAJLÁTH, Csilla [HU/HU]; Átlós u. 174, H-1204 Budapest (HU). MOLNÁR, Péter [HU/HU]; Rigómező u. 1, H-2143 Kistarcsa (HU). PODÁNYI, Benjamin [HU/HU]; Kazinczy u. 29, H-2120 Dunakeszi (HU). RITZ, Imola [HU/HU]; Erdősor u. 11/15, H-1046 Budapest (HU). SÁNTÁNÉ, Csutor, Andrea [HU/HU]; Szárnyas u. 22/c, H-1107 Budapest (HU). SZÓKÉNÉ, Szappanos, Andrea [HU/HU]; Üllői u. 120-122, H-1101 Budapest (HU). SZVOBODA, Györgyné [HU/HU]; Váczi M. u. 21, H-2120 Dunakeszi (HU).

(74) Common Representative: CHINOIN GYÓGYSZER ÉS VEGYÉSZETI TERMÉKEK GYÁRA RT.; Iparjogi Osztály, Tó u. 1-5, H-1045 Budapest (HU).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: QUINOXALINE COMPOUNDS, PHARMACEUTICAL PREPARATIONS CONTAINING THEM AND A PROCESS FOR THE PREPARATION THEREOF

(57) Abstract

The invention relates to compounds of general formula (I) and salts, tautomeric forms and N-oxides thereof in which formula: Z^1 means hydrogen, hydroxy, C_{1-4} alkyl, C_{7-9} phenylalkyl, optionally substituted phenyl, $COOC_{1-4}$ alkyl, C_{2-14} acyl, C_{1-4} alkylsulphonyl, trifluoromethyl-sulphonyl, optionally substituted benzoyl, optionally substituted phenyl-sulphonyl group; Y^1 means hydrogen, or optionally substituted amino group, or Y^1 and Z^1 form together a -CO-O- group, where Y^2 and Z^2 mean together a valency bond, or Y^1 and Y^2 mean together a valency bond, and at the same time Z^2 means hydrogen, hydroxy, C_{1-4} alkyl, C_{7-9} phenylalkyl, optionally substituted phenyl, $COOC_{1-4}$ alkyl, C_{2-14} acyl, C_{1-4} alkylsulphonyl, trifluoromethyl-sulphonyl, optionally substituted benzoyl, optionally substituted phenyl-sulphonyl group; X^1 and X^2 mean together =O, or =S, or X^1 means hydrogen, -NHR^4 or -WR^5 groups, and at the same time X^2 means hydrogen, or X^2 and X^3 together form a valency bond, X^3 means hydrogen, C_{1-4} alkyl, C_{7-9} phenylalkyl, optionally substituted phenyl, R^1 and R^2 mean hydrogen, halogen, C_{1-4} alkyl, trifluoromethyl, ciano, mercapto or sulphonylamido group, R^3 means hydrogen or nitro group, R^4 means hydrogen or hydroxy group, R^5 means hydrogen, C_{1-4} alkyl, C_{7-9} phenylalkyl group, W means oxygen or sulfur with the proviso, that a) if at least one of the substituents of R^1, R^2 and R^3 is different from hydrogen or b) if the meaning of Z^1 and Z^2 is hydrogen and R^1 means 6-chloro, R^3 means hydrogen, R^2 has a different meaning from 7-chloro, or R^1 means 6-methyl, R^3 means hydrogen, R^2 has a different meaning from 7-methyl; compounds of general formula (I) show a significant activity at the glycine binding site of the NMDA-receptor, therefore they can be used as active ingredients of pharmaceutical compositions.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	**GB**	United Kingdom	**MW**	Malawi
AT	Austria	**GE**	Georgia	**MX**	Mexico
AU	Australia	**GN**	Guinea	**NE**	Niger
BB	Barbados	**GR**	Greece	**NL**	Netherlands
BE	Belgium	**HU**	Hungary	**NO**	Norway
BF	Burkina Faso	**IE**	Ireland	**NZ**	New Zealand
BG	Bulgaria	**IT**	Italy	**PL**	Poland
BJ	Benin	**JP**	Japan	**PT**	Portugal
BR	Brazil	**KE**	Kenya	**RO**	Romania
BY	Belarus	**KG**	Kyrgystan	**RU**	Russian Federation
CA	Canada	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CF	Central African Republic			**SE**	Sweden
CG	Congo	**KR**	Republic of Korea	**SG**	Singapore
CH	Switzerland	**KZ**	Kazakhstan	**SI**	Slovenia
CI	Côte d'Ivoire	**LI**	Liechtenstein	**SK**	Slovakia
CM	Cameroon	**LK**	Sri Lanka	**SN**	Senegal
CN	China	**LR**	Liberia	**SZ**	Swaziland
CS	Czechoslovakia	**LT**	Lithuania	**TD**	Chad
CZ	Czech Republic	**LU**	Luxembourg	**TG**	Togo
DE	Germany	**LV**	Latvia	**TJ**	Tajikistan
DK	Denmark	**MC**	Monaco	**TT**	Trinidad and Tobago
EE	Estonia	**MD**	Republic of Moldova	**UA**	Ukraine
ES	Spain	**MG**	Madagascar	**UG**	Uganda
FI	Finland	**ML**	Mali	**US**	United States of America
FR	France	**MN**	Mongolia	**UZ**	Uzbekistan
GA	Gabon	**MR**	Mauritania	**VN**	Viet Nam

e.) for the preparation of compounds of the general formula ID, where the meanings of R^1, R^2, R^3 are as given above, compounds of the general formula IC, where the meanings of R^1, R^2, R^3 are as given above, are acylated with formic acid derivatives, then closed into a ring or reacted with dialkylcarbonate;

f.) for the preparation of compounds of the general formula IE, where the meanings of R^1, R^2, R^3 are as given above, an 1,2-diaminobenzene of general formula II, where the meanings of R^1, R^2, R^3 are as given above, is reacted with dihalogenic glyoxime;

g.) for the preparation of compounds of the general formula IF, where the meanings of R^1, R^2, R^3 are as given above, an 1,2-diaminobenzene of general formula II is reacted with oxalic acid diiminoester of general formula VII, where the meanings of R^1, R^2, R^3 and R^7 are as given above;

h.) for the preparation of compounds of the general formula IB containing a sulfur atom in place of W, where the meanings of R^1, R^2, R^3, Z^1 and Z^2 are as given above, a compound of the general formula IB containing oxygen in place of W or a compound of the general formula IF, where the meanings of R^1, R^2, R^3 are as given above, is reacted with reagents suitable for sulfur introduction, or the compound of the general formula IB containing a sulfur atom in place of W is prepared from an appropriate R^1, R^2, R^3 substituted 2,3-dichloroquinoxaline or 2,3-dithioquinoxaline derivatives by selective transformation;

i.) for the preparation of compounds of the general formula IG, where the meanings of R^1, R^2, R^3, Z^1, X^1, X^2, X^3 are as given above and the meaning of A is an optionally substituted amino group, compounds of the general formula IA, where the meanings of R^1, R^2, R^3 are as given above, W is an oxygen atom, are N-animated and

if desired in the compounds of the general formula I thus obtained, substituents R^1, R^2, R^3 and X^3 are transformed in a manner known per se into other R^1, R^2, R^3 and X^3 substituents, and/or into their N-oxides, and/or salts, and/or are deliberated from their salts.

Advantageously the preparation of the compounds of the general formula IA can be carried out by a method described in Tetrahedron Lett. 23 No.33, pp.3357-60 or J.C.S.96(1947).

For the preparation of compounds of the general formula IB containing alkyl, phenylalkyl or optionally substituted phenyl group in place of Z^1 the reaction is advantageously carried out in a polar solvent, advantageously in lower alcohol, in dimethylformamide or in dimethylsulphoxide, or in an apolar solvent such as tetrahydrofuran, between 0°C and boiling point, advantageously between 20 and 80°C.

Compounds of the general formula IB containing acyl, alkylsulphonyl, trifluoromethylsulphonyl, optionally substituted phenylsulphonyl group in place of Z^1 and/or Z^2 can be prepared advantageously by reacting the compound of general formula IB, containing hydrogen atom in place of Z^1 and/or Z^2 with an acylating agent optionally in the presence of a proton acceptor. It is advantageous to use acid anhydride as acylating agent and perform the reaction without a proton acceptor.

According to the invention it is advantageous to perform procedure e.) by applying methyl chloroformate as a formic acid derivative. The acylation is performed under mild conditions and a basic catalyst is applied for the ring closure. It is advantageous to perform the reaction of compounds of the general formula IC and dialkylcarbonates in a weak basic medium.

It is advantageous to perform the reaction of compounds of the general formula II and dihalogeno glyoximes /(Chem.Ber.85 3 5,(1952)/ in a biphasic system, in the presence of a proton acceptor /(J. Het.Chem..26 1415 (1989)/.

Based on the literature of J. Org. Chem. Vol. 21, pp. 470, (1956), compounds of the general formula IB containing a sulfur atom in place of W can be synthesized from appropriately substituted quinoxaline 2,3-diones, advantageously in excess of ammonia or a primary amine, optionally in the presence of a solvent.

Description of biological test methods

^{3}H-dichlorokinurenic acid (DCK) binding assay

[^{3}H]DCK (10nM) binding was examined by the method of T. Canton and his collaborators (J. Pharm. Pharmcol., 44 812-816, (1992). After removal of the cerebellum and the brain stem from the whole brain of 150-200 g male rats (Sprague-Dawley) a membrane preparation was made by homogenization and repeated centrifugation. Incubation was done for 30 minutes at 4°C in 50 mM HEPES/KOH buffer (pH=7.5) in the presence and absence of test substances. Radio ligand bound to the membrane was separated by filtration method (Whatman GF&B). Bound radioactivity was measured by liquid scintillation spectrophotometer. Non-specific binding was determined in the presence of 1 mM glycine. The percent of binding was determined by the following formula:

$$[1-\{B_i\text{-NSP})/(B_t\text{-NSP})\}]X100, \text{ where}$$

B_i is the binding measured in the presence of the test substance

B_t total binding measured in the absence of the test substance

NSP non-specific binding

Table I contains the tested substances and their 50% binding causing concentration (IC_{50} value).

Table I.

Test number	Name	IC_{50} (nM)
control	6-trifluoromethyl-quinoxaline-2,3-dione	4000
7	3-amino-6-trifluoromethyl-7 chloro-8-nitro-quinoxaline-2-one	161
6	3-amino-6,7-dichloro-8-nitro-quinoxaline-2-one	91
48	3-lauroylamido-6,7-dichloro-8-nitro-quinoxaline-2-one	54

Compounds of the general formula I or their salts may be used in the therapy as pharmaceutical preparations containing the active ingredient and inert solid or liquid organic or inorganic excipients. Manufacturing of the preparations takes place according to known methods.

Preparations are made in forms suited for oral or parenteral application e.g. tablet, coated tablet, capsule, or their retard versions. The preparations may contain appropriate solid diluting or carrier substances, sterile aqueous solvent or non-toxic organic solvent. For such purpose sweetening and flavoring substances can be added to oral preparations.

Tablets suitable for oral application may contain lactose, sodium citrate, calcium carbonate as carrier substances, and substances promoting disintegration (e.g. starch, alginic acid), lubricants (e.g. talc, sodium laurylsulfate, magnesium stearate). Carrier substances of capsules may be lactose and polyethylene glycol. Aqueous suspensions may contain emulsifying and suspending agents. Diluting agents of the organic solvent suspensions may be ethanol, glycerin, chloroform, etc.

Preparations suitable for parenteral application are solutions or suspensions of the active ingredient in an appropriate medium (e.g. hazelnut oil, sesame oil, polypropylene glycol or water).

The active ingredient content of the pharmaceutical preparations can change within wide ranges, it may be between 0.005-99%.

The daily dose of the active ingredient can change within wide ranges and depends on the severity of the condition, age, body weight of the patient, form of the preparation and activity of the given active ingredient. In case of oral dosage, the daily active ingredient dose is generally 0.5-20 mg/kg in a single dose or in daily multiple doses. The above data is of informational character from which in a given case and depending on instructions of the physician it can be deviated up or down.

Further details of the invention are given in the following examples without limiting it.

Example 2

Introduction of the nitro group:

The product of example 1 resp. 4 is dissolved in concentrated sulfuric acid and treated with 1-1.2 equivalent KNO_3 at a temperature of 0 to 5°C. The endpoint of the reaction is determined by TLC from the sample taken from the mixture. In case of complete reaction the reaction mixture is poured on ice 5-15 fold of the volume of the sulfuric acid used as solvent and the precipitated substance is filtered.
Physical data of the substances thus obtained are identical with the data of examples 6 and 7 listed in Table I.

Example 3

The products of examples 1 and 4 may also be nitrated by treating their water free „Sulfolanic" suspension with nitronium tetrafluoroborate at a temperature of max. 20°C. Processing of the obtained products and their physical data are identical with those of example 2.

Example 4

Treating compounds of the general formula IF (J. Am. Chem. Soc. **68.** 1035 (1946)) with 2.5-5 M aqueous hydrochloric acid for a short time at 100-120°C results compounds of IA. Isomers can be separated by e.g. flash vacuum chromatography. Table III summarizes physical data and yields of the compounds prepared.

Table III

No.	R1	R2	R3	%	*	Mp. (°C)	Characteristic chemical shifts by NMR
16	5-Cl	H	7-Cl	20	-	>310	See table VI
17	H	6-Cl	8-Cl	30	-		See table VI
18	H	6-SCN	7-F	57	82	>260	5,8-H: 7.58, 7.09
19	H	6-F	7-SCN		18		5,8-H: 7.40, 7.26
20	H	6-SCN	7-Cl	39	62		5,8-H: 7.62, 7.31
21	H	6-Cl	7-SCN		38		5,8-H: 7.51, 7.47

* Isomeric ratios were determined by NMR.

In case of separated isomers the identification of regio isomers was performed by C^{13} NMR. Bread bound decoupled and proton coupled C^{13} spectra of both pure isomers were made and for the identification of C^{13}-^1H coupling constants with long range effects selective INEPT measurement series were made. With the knowledge of the C^{13}-^1H coupling constants with long range effects chemical shifts of carbon atoms in different positions of both isomers were identified in the heteroatom free aromatic ring and they were compared to the two hydrogen atoms. It is known that the effect of the amide and imino group on the chemical shift influencing effect of aromatic carbon atoms is characteristically different (E. Pretsch, J. Seibl, W. Simon, T. Clerc: Tabellen zur Strukturaufklärung organischer Verbindungen mit spektroskopischen Methoden, Springer, Berlin (1981)). On carbon atoms in ipso and ortho position to the amide group a smaller deviation is expected than on carbon atoms having the same position to an imino group. The two sets of signals were matched with the isomers given in table IV by comparing the values measured for these carbon atoms in the two compounds. In case of the other not separated isomeric mixtures the isomers were matched based on chemical shifts of these characteristic signs. The ratio of the isomers was determined from the intensity of the signals.

Table IV

	6-Cl, 8-Cl	5-Cl 7-*Cl
(C-4a)	135.9	129.6
(C-5)	122.5	128.3
(C-6)	126.9	123.1
(C-7)	122.6	126.3
(C-8)	119.0	113.6
(C-8a)	125.0	130.7

Example 5

Preparation of compounds of the general formula IC

Preparation and transformation of compounds of the general formula VI

0.1 M 1,2-diaminobenzene derivative of the general formula II is dissolved/suspended in 20 cm^3 methanol and 8.75 cm^3 36% hydrochloric acid solution are added to it. The solution thus formed is cooled to below 10°C and 1.05 M potassium cyanide are added to it dropwise while constantly stirring. The pH of the reaction mixture is adjusted to 6.5 and 8.90 g 35% formaldehyde solution are added to it dropwise at 40°C in 20 to 35 minutes. It is cooled to 0°C after 2 hours and the precipitated material is separated from the aqueous alcoholic mother liquor either by filtration or by extraction following an aqueous dilution.

The thus formed raw material of the general formula VI are boiled without any purification in a 60% aqueous alcoholic solution of 0.2 M hydroxylamine base for 3 to 5 hours until ammonia evolution ceases. The solution is cooled after clarification, let stand in the refrigerator and the precipitated crystals are filtered.

Table V contains the melting points and the yields.

Table V

No.	R^1	R^2	R^3	%	Mp. (°C)
22	H	6-Cl	7-Cl	90	190-191
23	H	6-Cl	7-CF_3	65	

Example 6

Preparation of compounds with the general formula ID

10 mmole IC compound are dissolved in 15 to 20 cm^3 acetone and 11 mmole triethylamine are added to it and the reaction mixture is treated with 10.5 mmole methyl chloroformate between 0 and 25°C. After the removal of triethylamine hydrochloride compounds of the general formula ID are crystallized.

Yields and physical data are summarized in table VI.

No.	R^1	R^2	R^3	%	Mp. (°C)
24	H	7-Cl	8-Cl	91	214-218

Example 7

Preparation of compounds of the general formula IE

5 mmole substituted 1,2-diaminobenzene of the general formula II and 5.2 mmole dichloroglyoxime are suspended in 25 cm^3 dichloromethane, then 50 mmole Na_2CO_3 dissolved in 25 cm^3 distilled water are added to it dropwise, and the mixture is rigorously stirred for 1 hour. (The reaction is followed by TLC). The precipitated substance is filtered, washed with water and dichloromethane and purified by chromatography if necessary.

Table VII contains data of the obtained compounds.

Table VII.

No.	R^1	R^2	R^3	%	Hydrate water	Mp. (°C)
25	5-Cl	H	7-Cl	45	1	231
26	H	6-Cl	7-Cl	40	-	240

Example 8

Preparation of compounds of the general formula IB containing an oxygen atom in place of W.

a./ 8 mmole substituted 1,2-diaminobenzene of the general formula II are dissolved in 12 cm^3 THF. By keeping the temperature of the mixture at ~10°C 10 mmol imidoyl chloride of general formula IV are added to it. After standing at room temperature for 1 day, the precipitated substance is filtered, washed with ethanol, purified by chromatography if necessary.

Table VIII

No.	R^1	R^2	R^3	Z^1	%	*	Mp. (°C)	Characteristic chemical shifts by NMR
27	H	6-Cl	7-Cl	CH_3	38		>300**	
28	H	6-Cl	8-Cl	CH_3	38		262-265**	
29	H	6-SO_2NH_2	7-Cl	CH_3	40	92	>300	C-5:124.9 C-8 117.1
30	H	6-Cl	7-SO_2NH_2	CH_3		8		C-5:126.0 C-8:116.3
31	H	6-CF_3	7-Cl	CH_3	59	90		C-5 119.0 C-8:118.0
32	H	6-Cl	7-CF_3	CH_3		10	267-270**	C-5:122.4 C-8 115.1
33	H	6-Br	8-Br	CH_3	55		265	
34	H	6-Cl	7-Cl		65		239-241	
35	H	6-Cl	7-Cl	Ph	71		276-281	
36	H	6-SO_2NH_2	8-Br	CH_3	35		279-283	

* Isomeric ratios were determined by ^{13}CNMR.

** HCL salt

b./ Preparation of nitro compounds of the general formula IB containing an oxygen atom in place of W can be carried out according to examples 2 or 3.

Table IX

No.	R^1	R^2	R^3	Z^1	%	*	Mp. (°C)	Characteristic chemical shifts by NMR
37	8-NO_2	6-Cl	7-Cl	CH_3		93		5-H: 7.68
38	5-NO2	6-Cl	7-Cl	CH_3	60	7	273-276	8-H: 7.36
39	8-Cl	6-Cl	7-NO_2	CH_3		88		C-5:123.7: C-8:111.1
40	5-NO_2	6-Cl	7-Cl	CH_3	89	12	308	C-5:142.4: C-8: 120.4
41	8-NO_2	6-Cl	7-CF_3	CH_3	51		267-279	

* Isomeric ratios were determined by NMR.

Example 9

Preparation of compounds of the general formula IB containing an oxygen atom in place of W

a./ 1 mmol acid anhydride is added to 0.35 mmole of the product of examples 1. resp 8.. The mixture is boiled until reaction takes place, evaporated and the product is recrystallized from ethanol.

Table X.

No.	R^1	R^2	R^3	Z^1	Z^2	%	*	Mp. (°C)	Characteristic chemical shifts by NMR
42	H	6-Cl	7-Cl	CH_3	Ac	98		254-247	
43	H	6-CF_3	7-Cl	CH_3	Ac		96		5.8-H: 8.12. 7.50
44	H	6-Cl	7-CF_3	CH_3	Ac	80	4	239-241	5.8-H: 8.05. 7.72
45	H	6-Cl	7-Cl	H	Ac	76		306	
46	H	6-CF_3	7-Cl	H	Ac	95		266-268	
47	6-CF_3	7-Cl	8-NO_2	H	Ac	85		205	

* Isomeric ratios were determined by NMR.

b./ Compounds prepared according to examples 1 and 2 are dissolved in aceton, and acylated in the presence of a proton acceptor and with equivalent + 10% acid halogenide at room temperature. The substance obtained after aqueous dilution or evaporation in vacuo is recrystallized.

Table XI.

No.	R^1	R^2	R^3	Z^1	%	Mp. (°C)
48	6-Cl	7-Cl	8-NO_2	$C_{11}H_{23}CO$-	74	113
49	6-CF_3	7-Cl	8-NO_2	CH_3SO_2-	81	185
50	6-Cl	7-Cl	8-NO_2	B_Z	60	272
51	6-Cl	7-Cl	8-NO_2	$C_5H_{11}CO$	90	215-218
52	6-Cl	7-Cl	8-NO_2	$C_{15}H_{31}CO$	64	105-108

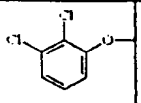
Example 10

Preparation of substances of the general formula IF

0.1 mol 1,2-diaminobenzene derivative is dissolved in 3 to 10 times methanol (ethanol, DMSO) and 1.15 mol oxalic acid diimid dimethylester and 3 to 5 mmole p-toluene sulfonic acid are added to it as a catalyst. The reaction mixture is let stand at room temperature for 5 to 20 hours, the precipitated substance is filtered and washed with alcohol. The following table contains substances thus prepared.

For other starting material see Chem. Ber. 97 1599 (1964)

Table XII

No.	R^1	R^2	R^3	%	Mp. (°C)
53	H	6-Cl	7-Cl	80	>315
54	H	6 	7-Cl	43	243-247
55	5-Cl	H	7-Cl	42	>300
56	H	6-Cl	7-SCN	85	>270
57	H	6-F	7-SCN	62	>270

Example 11

Preparation of compounds of the general formula IB containing a sulfur atom in place of W

10 cm^3 abs. ethanol saturated with ammonia is added to 0.5 g 6-trifluoromethyl-7-chloro-2,3-quinoxaline-dithione. The reaction mixture is kept in closed vessel for 5 days at room temperature. It is purified by "flash" vacuum chromatography /J. Org. Chem. 44, 4963 (1979); MKL 40, 366 (1985)/..

Table XIII

No.	R^1	R^2	R^3	Z^1	%	*	Mp. (°C)	Characteristic chemical shifts by NMR
58	H	6-Cl	7-CF_3	H		88		C-5=126.4; C-8=115.4
	H	6-CF_3	7-Cl	H	32	12	260	C-5=123.9; C-8=117.9
59	H	6-Cl	7-CF_3	CH_3		82		C-5=126.4; C-8=115.1
	H	6-CF_3	7-Cl	CH_3	41	18	250-255	C-5=123.8; C-8=117.0
60	H	6-Cl	7-Cl	Ph	25		275-280	C-5=126.8; C-8=116.9

* Isomeric ratios were determined by NMR.

Example 12

Preparation of compounds of the general formula IG

a./ 0.4 g (1.5 mmole) O-tosyl-acetoxy-hydroxamate are added to 2 cm^3 60% perchloric acid, mixed at room temperature for 20 minutes, poured on ice, then extracted with 2x1 cm^3 dichloromethane. The solution thus obtained, which contains approximately 0.2 g (1.1 mmole) O-tosyl-hydroxylamine is added to the suspension of 1 mmol 3-amino-quinoxaline-2 one derivative and 50 mg (1.25 mmole) sodium hydride (60% dispersion in mineral oil) in 5 cm^3 DMF, mixed at room temperature for 2 hours, then worked up. The base is released from the tosylate salt by aqueous sodium carbonate treatment.

Table XIV

No.	R^1	R^2	R^3	X^3	X^1 and X^2	A	%	Mp. (°C)
61	H	6-Cl	7-Cl	H	O	NH_2	80	310-312*
62	H	6-Cl	7-Cl	H	O	NH_2	98	280-282**

* Tosylate salt

** monohydrate

b./ Compounds of the general formula IA -where the meaning of W is an oxygen atom -are reacted with alkyl halogenides in DMF in the presence of K_2CO_3.

Table XV

No.	R^1	R^2	R^3	X^3	X^1 and X^2	A	%	Mp. (°C)
63	H	6-Cl	7-Cl	$C_{12}H_{25}$	O	H	90	123-125

Example 13

Preparation of compounds of the general formula IB, where W=O and Z_1=OH; Z_2=H

4.6 mmole 1,2-diaminobenzene of the general formula II are dissolved in 10 cm^3 ethanol. 4.6 mmole (0.7 g) chloro-oximino-ethyl-acetate are added to it. After dissolution while constantly stirring 4.6 mmole $NaHCO_3$ dissolved in 5 cm^3 distilled water are added to it dropwise. After standing over night, the precipitated substance is filtered, washed with water and purified if necessary.

Table XVI contains data of the obtained compounds.

Table XVI

No	R^1	R^2	R^3	%	Mp. (°C)
64	H	H	H	85	256-259
65	H	6-Cl	7-Cl	93	286-287
66	H H	$6CF_3$ 6-Cl	7-Cl $7-CF_3$	81	277-280
67	H 5-Cl	6-Cl H	8-Cl 7-Cl	86	decomposition over 240
68	6-Cl	7-Cl	$8-NO_2$	55	276-277
69	6-Cl	7-Cl	8-Cl	60	decomposition over 254

Example 14

Compounds of the general formula ID containing an oxo-group in position 4 may be prepared according to example 6.

Table XVII contains data of the obtained compound.

Table XVII

No	R^1	R^2	R^3	%	Mp. (°C)
70	H	H	H	75	274-277

Claims

1.) Compounds of the general formula I and salts, tautomeric forms and N-oxides thereof in which formula:

Z^1 means hydrogen, hydroxy, C_{1-4} alkyl, C_{7-9} phenylalkyl, optionally substituted phenyl, $COOC_{1-4}$ alkyl, C_{2-14} acyl, C_{1-4} alkylsulphonyl, trifluoromethyl-sulphonyl, optionally substituted benzoyl, optionally substituted phenyl-sulphonyl group;

Y^1 means hydrogen, or optionally substituted amino group, or

Y^1 and Z^1 form together a -CO-O- group, where

Y^2 and Z^2 mean together a valency bond, or

Y^1 and Y^2 mean together a valency bond, and at the same time

Z^2 means hydrogen, hydroxy, C_{1-4} alkyl, C_{7-9} phenylalkyl, optionally substituted phenyl, $COOC_{1-4}$ alkyl, C_{2-14} acyl, C_{1-4} alkylsulphonyl, trifluoromethyl-sulphonyl, optionally substituted benzoyl, optionally substituted phenyl-sulphonyl group;

X^1 and X^2 mean together =O, or =S, or

X^1 means hydrogen, $-NHR^4$ or $-WR^5$ groups, and at the same time

X^2 means hydrogen, or

X^2 and X^3 together form a valency bond,

X^3 means hydrogen, C_{1-4} alkyl, C_{7-9} phenylalkyl, optionally substituted phenyl,

R^1 and R^2 mean hydrogen, halogen, C_{1-4} alkyl, trifluoromethyl, ciano, mercapto or sulphonylamido group,

R^3 means hydrogen or nitro group,

R^4 means hydrogen or hydroxy group,

R^5 means hydrogen, C_{1-4} alkyl, C_{7-9} phenylalkyl group,

W means oxygen or sulfur

with the proviso, that

a.) if at least one of the substituents of R^1, R^2 and R^3 is different from hydrogen or

b.) if the meaning of Z^1 and Z^2 is hydrogen and

- R^1 means 6-chloro, R^3 means hydrogen

R^2 has a different meaning from 7-chloro, or

- R^1 means 6-methyl, R^3 means hydrogen.
  R^2 has a different meaning from 7-methyl.

2.) Compounds of the general formula IA, IB, IC, ID, IE, IF, IG, their salts, tautomeric forms and N-oxides,
where the meaning of R^1, R^2, R^3, Z^1, X^1, X^2, X3 are given in claim 1, W means a sulfur or an oxygen and the meaning of A is an optionally substituted amino group.

3.) Compounds according to claim 1):
3-amino-6,7-dichloro-8-nitro-quinoxaline-2-one
3-amino-6-trifluoromethyl-7-chloro-8-nitro-quinoxaline-2-one
3-acetylamido-6,7-dichloro-8-nitro-quinoxaline-2-one
3-lauroylamido-6,7-dichloro-8-nitro-quinoxaline-2-one
3-methylsulfonamido-6-trifluoromethyl-7-chloro-8-nitro-quinoxaline-2-one

4.) Process for the preparation of compounds of the general formula I, characterized that:
a.) for the preparation of compounds of the general formula IA - where the meanings of R^1, R^2, R^3 and W are as given above - an 1,2-diaminobenzene of the general formula II is reacted with a carboalkoxyformimidate derivative of the general formula III - where the meanings of R^1, R^2, R^3 and W are as given above, R^6 means hydrogen, R^7 means C_{1-2} alkyl; or compounds of the general formula IF, where R^1, R^2, R^3 have the meanings as given above are hydrolyzed in acidic medium;

b.) for the preparation of compounds of the general formula IB - where the meanings of R^1, R^2, R^3 and W are as given above, Z^2 means hydrogen and Z^1 means C_{1-4} alkyl, C_{7-9} phenylalkyl, or optionally substituted phenyl group - an 1,2-diaminobenzene of the general formula II is reacted with a compound of the general formula IV - where the meanings of R^1, R^2, R^3, R^7 and W are as given above, Hlg means halogen, R^8 means C_{1-4} alkyl, C_{7-9} phenylalkyl, or optionally substituted phenyl group, R^7 means C_{1-2} alkyl group;

c.) for the preparation of compounds of the general formula IB - where the meanings of R^1, R^2, R^3, W and Z^1 are as given above, Z^2 means C_{2-14} acyl, C_{1-4} alkylsulphonyl, trifluoromethylsulphonyl, optionally substituted benzoyl, optionally substituted phenylsulphonyl group - compounds of the general formula IB containing hydrogen atom in place of Z^2 are reacted with acylating agents of the general formula Z^2-L, where the meaning of Z^2 is C_{2-14} acyl, C_{1-4} alkylsulphonyl, triflouromethylsulphonyl, optionally substituted benzoyl, optionally substituted phenylsulphonyl group and the meaning of L is a leaving group;

d.) for the preparation of compounds with the general formula IC, where the meanings of R^1, R^2, R^3 are as given above, an 1,2-diaminobenzene of the general formula II, where the meanings of R^1, R^2, R^3 are as given above, is cianomethylated, then the intermediate of general formula VI thus obtained is closed into a ring with hydroxylamine;

e.) for the preparation of compounds of the general formula ID, where the meanings of R^1, R^2, R^3 are as given above, compounds of the general formula IC, where the meanings of R^1, R^2, R^3 are as given above, are acylated with formic acid derivatives, then closed into a ring or reacted with dialkylcarbonate;

f.) for the preparation of compounds of the general formula IE, where the meanings of R^1, R^2, R^3 are as given above, an 1,2-diaminobenzene of general formula II, where the meanings of R^1, R^2, R^3 are as given above, is reacted with dihalogene glyoxime;

g.) for the preparation of compounds of the general formula IF, where the meanings of R^1, R^2, R^3 are as given above, an 1,2-diaminobenzene of general formula II is reacted with oxalic acid diiminoester of general formula VII, where the meanings of R^1, R^2, R^3 and R^7 are as given above;

h.) for the preparation of compounds of the general formula IB containing a sulfur

atom in place of W, where the meanings of R^1, R^2, R^3, Z^1 and Z^2 are as given above, a compound of the general formula IB containing oxygen in place of W or a compound of the general formula IF, where the meanings of R^1, R^2, R^3 are as given above, is reacted with reagents suitable for sulfur introduction, or the compound of the general formula IB containing a sulfur atom in place of W is prepared from an appropriate R^1, R^2, R^3 substituted 2,3-dichloroquinoxaline or 2,3-dithioquinoxaline derivatives by selective transformation;

i.) for the preparation of compounds of the general formula IG, where the meanings of R^1, R^2, R^3, Z^1, X^1, X^2, X^3 are as given above and the meaning of A is an optionally substituted amino group, compounds of the general formula IA, where the meanings of R^1, R^2, R^3 are as given above, W is an oxygen atom, are N-animated and

if desired in the compounds of the general formula I thus obtained, substituents R^1, R^2, R^3 and X^3 are transformed in a manner known per se into other R^1, R^2, R^3 and X^3 substituents, and/or into their N-oxides, and/or salts, and/or are deliberated from their salts.

5.) Pharmaceutical preparations containing as active ingredient a compound of general formula I, wherein

Z^1 means hydrogen, hydroxy, C_{1-4} alkyl, C_{7-9} phenylalkyl, optionally substituted phenyl, $COOC_{1-4}$ alkyl, C_{2-14} acyl, C_{1-4} alkylsulphonyl, trifluoromethyl-sulphonyl, optionally substituted benzoyl, optionally substituted phenyl-sulphonyl group;
Y^1 means hydrogen, or optionally substituted amino group, or
Y^1 and Z^1 form together a -CO-O- group, where
Y^2 and Z^2 mean together a valency bond, or
Y^1 and Y^2 mean together a valency bond, and at the same time
Z^2 means hydrogen, hydroxy, C_{1-4} alkyl, C_{7-9} phenylalkyl, optionally substituted phenyl,

$COOC_{1-4}$ alkyl, C_{2-14} acyl, C_{1-4} alkylsulphonyl, trifluoromethyl-sulphonyl, optionally substituted benzoyl, optionally substituted phenyl-sulphonyl group;

X^1 and X^2 mean together =O, or =S, or

X^1 means hydrogen, $-NHR^4$ or $-WR^5$ groups, and at the same time

X^2 means hydrogen, or

X^2 and X^3 together form a valency bond,

X^3 means hydrogen, C_{1-4} alkyl, C_{7-9} phenylalkyl, optionally substituted phenyl,

R^1 and R^2 mean hydrogen, halogen, C_{1-4} alkyl, trifluoromethyl, ciano, mercapto or sulphonylamido group,

R^3 means hydrogen or nitro group,

R^4 means hydrogen or hydroxy group,

R^5 means hydrogen, C_{1-4} alkyl, C_{7-9} phenylalkyl group,

W means oxygen or sulfur

with the proviso, that

a.) if at least one of the substituents of R^1, R^2 and R^3 is different from hydrogen or

b.) if the meaning of Z^1 and Z^2 is hydrogen and

- R^1 means 6-chloro, R^3 means hydrogen
  R^2 has a different meaning from 7-chloro, or
- R^1 means 6-methyl, R^3 means hydrogen,
  R^2 has a different meaning from 7-methyl.

6.) Pharmaceutical preparation according to claim 5.) comprising as active ingredient one or more of the compounds, tautomeric forms, salts and /or N-oxides thereof:

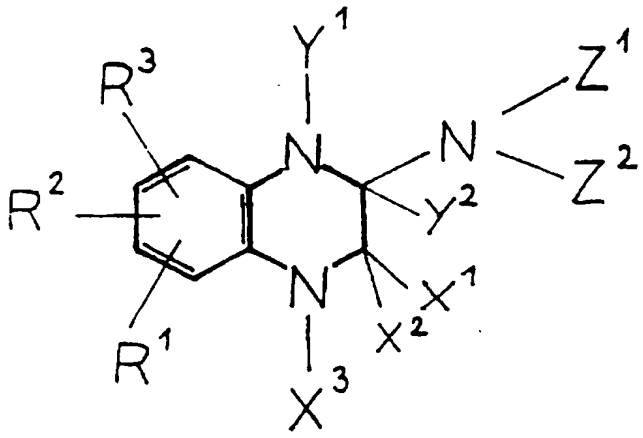
3-amino-6,7-dichloro-8-nitro-quinoxaline-2-one

3-amino-6-trifluoromethyl-7-chloro-8-nitro-quinoxaline-2-one

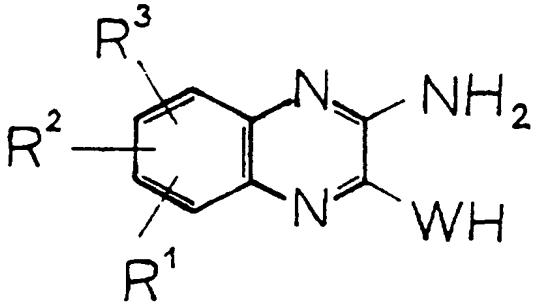
3-acetylamido-6,7-dichloro-8-nitro-quinoxaline-2-one

3-lauroylamido-6,7-dichloro-8-nitro-quinoxaline-2-one

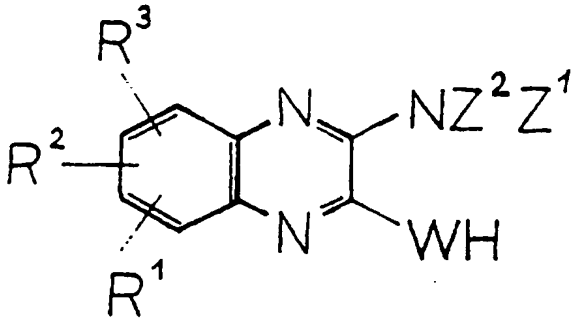
3-methylsulfonamido-6-trifluoromethyl-7-chloro-8-nitro-quinoxaline-2-one



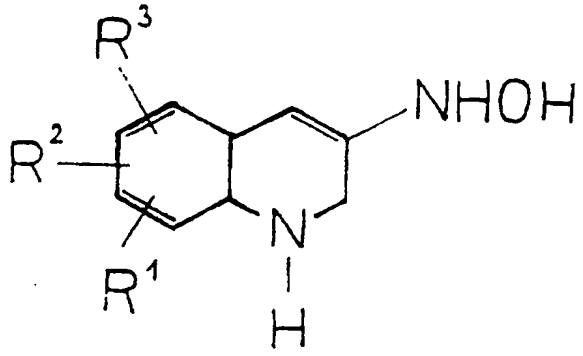
I.



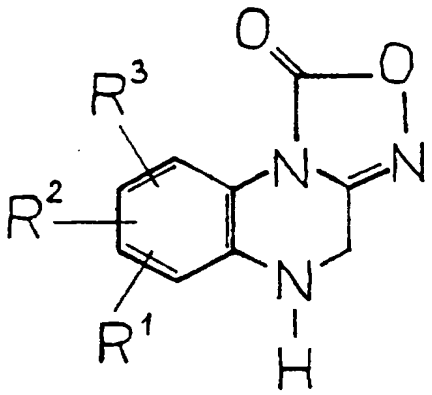
IA.



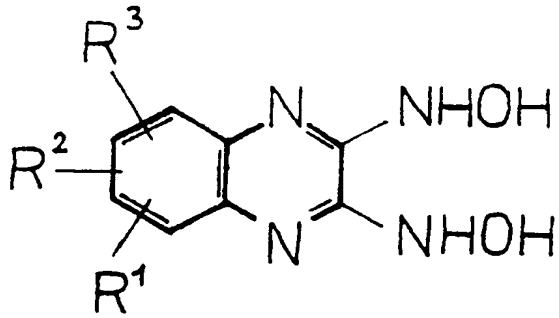
IB.



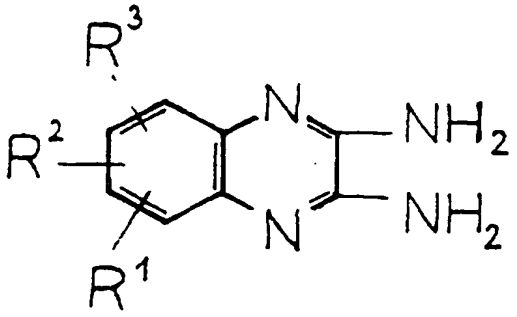
IC.



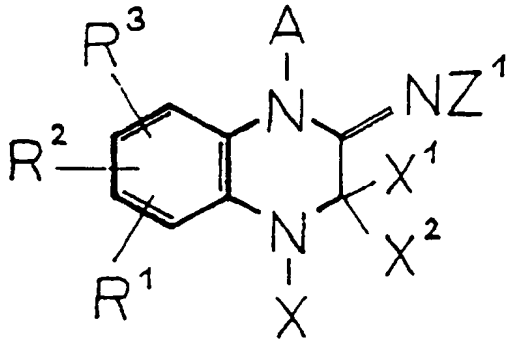
ID.



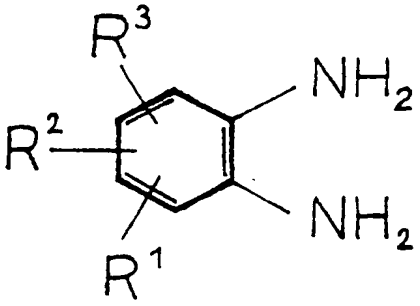
IE.



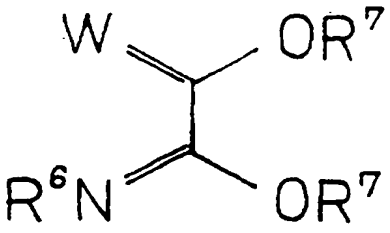
IF.



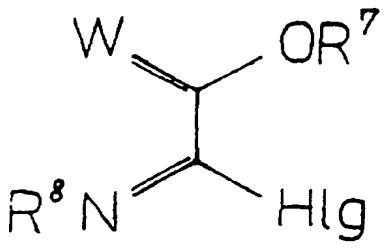
IG.



II.



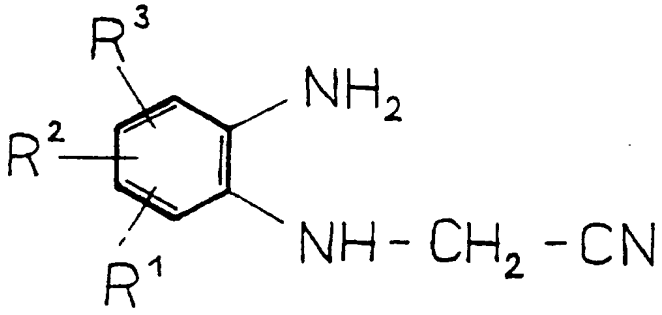
III.



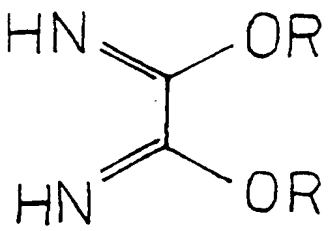
IV.

$$Z^{2'} - L$$

V.



VI.



VII.

INTERNATIONAL SEARCH REPORT

Inte nal Application No
PCT/HU 96/00072

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D241/44 C07D498/04 C07D241/54

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3 446 809 A (R.HARRIS ET AL.) 27 May 1969 see the whole document	1
X	EP 0 030 795 A (I.C.I.) 24 June 1981 see page 17 - page 31; claim 11; table 4	1,5
P,X	WO 96 04288 A (ACEA) 15 February 1996 see page 89 - page 91; claims; figure XLIX	1,5
A	TETRAHEDRON LETTERS, vol. 23, no. 33, 1982, OXFORD GB, pages 3357-3360, XP002027397 A.MCKILLOP ET AL.: "HETEROCYCLIC SYNTHESIS USING ETHYL CARBOETHOXYFORMIMIDATE." cited in the application see page 3357 - page 3360	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 March 1997	26.03.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Francois, J

Form PCT/ISA/210 (second sheet) (July 1992)